

REMARKS

Claims 20-35 are pending in the application. Claims 20, 21, 23, 24, and 28-35 are rejected. Claims 22 and 25-27 are objected to. While no reason for the objection is provided by the Office Action, Applicants will assume that claims 22 and 25-27 are objected to as dependent upon a rejected base claim unless informed otherwise. Claim 35 also is objected to under 37 C.F.R. 1.75(c) as failing to further limit the subject matter of a previous claim. Applicants amend claims 23, 29 and 35. Accordingly, claims 20-35 remain pending upon entry of this Amendment and Response.

Amendment to the claims

Applicants have amended claims 23, 27, 29, 33, and 35. Specifically, claim 23 was amended to correct antecedent basis, claim 29 was amended to remove language from the preamble, claims 27 and 33 were amended to correct grammatical errors, and claim 35 was amended as requested by the Examiner and to remove language from the preamble of incorporated claim 29. Applicants submit that no new matter was added by this amendment.

Objection under 37 C.F.R. 1.75(c)

Claim 35 was objected to under 37 C.F.R. 1.75(c) as failing to further limit the subject matter of claims 29 or 30. The Office Action required that the claim be cancelled, amended to place the claim in proper dependent form, or rewritten in independent form. Applicants have rewritten claim 35 in independent form. Accordingly, Applicants request that the objection to claim 35 under 37 C.F.R. 1.75(c) be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 20, 21, 23, 24 and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the abstract of the article: Myslivecek *et al.*, NEUROSCIENCE 79(3): 659-669 (1997). Applicants adopt the Examiner's shortened title of "Myslivecek" to refer to this abstract for this Response.

The present inventors have discovered, surprisingly, that increasing NO levels via ecNOS causes an increase in blood flow through brain tissue that is not dependent on increases in blood pressure. The present invention employs this surprising discovery to provide increased cerebral bioavailability of physiologically active compositions.

Accordingly, both independent claims 20 and 21 recite, in relevant part, methods for increasing cerebral bioavailability of a physiologically active composition in an individual including administering the composition substantially contemporaneously with a NO-increasing agent or agents (claim 20), or a blood flow enhancing amount of L-arginine (claim 21).

The Examiner acknowledges that "Myslivecek does not specifically recite an increase in cerebral bioavailability of the physiologically active agent dopamine," but nonetheless argues that:

one skilled in the neurology art would have reasonably considered an improvement in learning and memory processing to have been the result of an increase in cerebral bioavailability of dopamine and NO. Such would have been obvious because Myslivecek teaches a dose dependent enhancement of learning and memory suggesting an increase in cerebral bioavailability of dopamine and NO.

Applicants disagree that dose-dependent enhancement of learning and memory would suggest an increase in cerebral bioavailability to one skilled in the art without the benefit of Applicants' own disclosure.

To establish a *prima facie* case of obviousness, a prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. MPEP 2142, *citing, In re Vaeck*, 947 F.2d 488 (Fed.Cir. 1991).

A *prima facie* case of obviousness has not been established, at least, because Myslivecek fails to disclose a method of increasing cerebral bioavailability of a physiologically active composition. The dose dependency of Myslivecek might have indicated to a skilled practitioner any of a variety of mechanisms. Prior to Applicants' own studies and resulting disclosure, however, the claimed method of increasing cerebral bioavailability was not known. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims over Myslivecek.

Claims 29-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract for the article: Werner *et al.*, PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 219(3): 171-182 (Dec. 1998). Applicants adopt the Examiner's shortened title of "Werner" to refer to this abstract for this Response.

Werner indicates that the underlying article is a review of studies investigating the role of tetrahydrobiopterin in the NO synthase reaction, and reports the observation that tetrahydrobiopterin ameliorates endothelial dysfunction in animals and humans. Werner concludes that the contribution of tetrahydrobiopterin (as a cofactor to NO synthases), to these observed effects is unclear.

In contrast, both amended independent claims 29 and 35 recite, in part: "[a] pharmaceutical composition comprising a blood-flow enhancing amount of an NO-increasing agent or agents which increases the production of NO by preexisting ecNOS and a physiologically active composition."

The Examiner acknowledges that "Werner fails to recite a composition comprising an NO-increasing agent or agents and at least one physiologically active agent," but nonetheless argues that:

[o]ne skilled in the art would have been motivated to prepare a composition comprising the NO-increasing agent or agents with various other physiological agents in view of Werner's teaching [of the requirement of various cofactors for NO synthases]. Such would have been obvious in the absence of evidence to the contrary because where the desirability of synthesizing nitric oxide is sought, Werner suggests the combination of L-arginine with various physiologically active co-factors.

Applicants respectfully disagree.

Werner does not teach or suggest all the claim limitations of claims 29 or 35 as required to establish a *prima facie* case of obviousness. MPEP 2142. For example, Werner does not teach or suggest a pharmaceutical composition, a blood-flow enhancing amount of an NO-increasing agent or agents and a physiologically active composition.

In addition, there is no suggestion or motivation, either in Werner or the knowledge generally available to one of ordinary skill in the art, to modify Werner as suggested by the Examiner. The mere fact that the co-factors studied in Werner *could* be administered with a physiologically active agent does not render this combination obvious at least because there is no teaching or suggestion in Werner to administer a

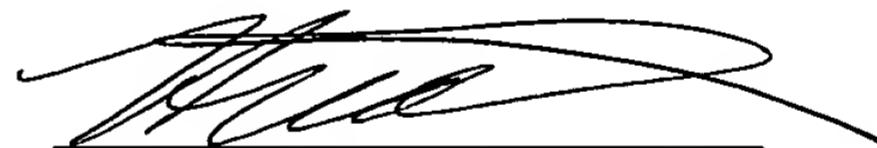
physiologically active composition with a NO-increasing agent or agents. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (emphasis added) MPEP 2143, *citing, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990).

Based on the foregoing, Applicants assert that Werner does not render independent claim 29, claims 30-34 depending from claim 29, or independent claim 35 obvious, at least because: (i) there is no suggestion or motivation to modify Werner as suggested by the Examiner; and (ii) Werner does not teach or suggest all of the claim limitations. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 29-35.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,



Danielle L. Herritt, Esq.
Reg. No. 43,670
for
DeAnn F. Smith, Esq.
Reg. No. 36,683
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400

Dated: May 23, 2003